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Abstract: Here, we present a case of a 50-year-old male with a history of a Guillain-Barré-syndrome, who was referred to our clinic with recurrent esophageal candidiasis and long-standing intermittent retrosternal cramps for further evaluation. Other symptoms such as dysphagia, regurgitations and weight loss were denied, and prior repeated endoscopy was otherwise unremarkable. Using high resolution impedance manometry, we could demonstrate a panesophageal pressure increase on water swallows and complete aperistalsis of the tubular esophagus, indicating achalasia type II. However, due to the patient's extraordinary body height and resulting length of the esophagus, endoluminal functional lumen imaging probe analysis supplementary to high resolution impedance manometry needed to be used to assess distensibility of the esophagogastral junction and to secure the diagnosis of achalasia before appropriately treating the patient with pneumatic dilation.

DOI: https://doi.org/10.1136/bcr-2017-221751

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TITLE OF CASE ***Do not include "a case report"***

Recurrent episodes of esophageal candidiasis without dysphagia post Guillain-Barré-Syndrome: An unusual presentation of Achalasia

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Key Words: Achalasia, Guillain-Barré-Syndrome, endoFLIP, pneumatic dilation, High Resolution Impedance Manometry, Integrated Relaxation Pressure

Abbreviations: EGJ: Esophagogastral junction, endoFLIP: endoluminal Functional Luminal Imaging Probe, GBS: Guillain-Barré-Syndrome, HRIM: High Resolution Impedance Manometry, IRP: Integrated Relaxation Pressure, LES: Lower esophageal sphincter, LAD: Left anterior descending artery (coronary artery)

SUMMARY ***Up to 150 words summarising the case presentation and outcome (this will be freely available online)***

Here we present a case of a 50-year-old gentleman with a history of a Guillain-Barré-Syndrome, who was referred to our clinic with recurrent esophageal candidiasis and longstanding intermittent retrosternal cramps for further evaluation. Other symptoms such as dysphagia, regurgitations and weight loss were denied and prior repeated endoscopy was otherwise unremarkable. Using high resolution impedance manometry, we could demonstrate a panesophageal pressure increase upon water swallows and

complete aperistalsis of the tubular esophagus, indicating achalasia type II. However, due to the patient's extraordinary body height and resulting length of the esophagus, endoFLIP analysis supplementary to high resolution impedance manometry needed to be used to assess distensibility of the esophagogastral junction and to secure the diagnosis of achalasia before appropriately treating the patient with pneumatic dilation.

BACKGROUND ***Also describe why you think this case is important – why did you write it up?***

Achalasia is a rare esophageal motility disorder characterized by aperistalsis and impaired relaxation of the lower esophageal sphincter (LES). The incidence of the disorder is estimated to be about 1.6 cases and prevalence about 10 cases per 100.000 population[1, 2]. The major clinical manifestations include dysphagia for both liquids and solids, retrosternal pain as well as instantaneous regurgitations upon deglutition and may be complicated by progressive weight loss[3]. Achalasia is caused by neurodegeneration of ganglion cells along the wall of the esophagus and the region of the LES, which is associated with inflammatory and fibrotic changes. Viral infections such as Herpes Simplex or Varicella Zoster triggering autoimmune processes are currently considered as the potential underlying pathogenesis of the disease[4-6]. Various autoimmune disorders such as Sjoegren Syndrome, Systemic Lupus or Rheumathoid Arthritis have all been associated with achalasia[7].

The gold standard in diagnosing achalasia is esophageal manometry, detecting functional obstruction at the level of the LES and aperistalsis of the esophageal body[8]. Recently, the endoluminal functional lumen imaging probe (endoFLIP) emerged as a new diagnostic modality, which measures the distensibility as well as the opening dynamics of the esophagogastral junction (EGJ). However, due to a current lack of data supporting its utility as well as a paucity of standardized protocols, its clinical relevance in large patient sets is yet to be confirmed[9].

Here we present a patient with history of a Guillain-Barré-Syndrome (GBS) developing achalasia with an atypical and unusual symptomatology.

CASE PRESENTATION ***Presenting features, medical/ social/ family history***

A 50-year-old 7 feet tall male was referred to our clinic with a history of recurrent esophageal candidiasis and progressive intermittent retrosternal cramps. The patient reported a history of GBS without respiratory insufficiency at age 18 and 38. At age 42, the patient developed intermittent periods of retrosternal cramps predominantly at night and independently of physical exertion or food intake. Dysphagia, regurgitations, heartburn, reflux symptoms and weight loss were denied. An extensive cardiologic workup showed an asymptomatic LAD stenosis without evidence of myocardial ischemia. Upper endoscopy was unremarkable except esophageal candidiasis, which was treated with fluconazole. Subsequent HIV testing showed a negative result. The patient's condition did not improve and the patient was repeatedly (age 45, 47, 49) scoped. Again, each time an esophageal candidiasis was found and treated with fluconazole, however without achieving relevant symptom amelioration. Due to recurrence of fungal infections of the esophagus, rare immunological disorders were ruled out with appropriate work up.

INVESTIGATIONS ***If relevant***

After referral to our clinic, we performed esophageal high resolution impedance manometry (HRIM) to assess a possible esophageal motor dysfunction. HRIM demonstrated complete aperistalsis and panesophageal pressure increase upon standardized assessment with single swallows as well as insufficient esophageal clearance, as assessed by impedance measurements during a provocation 200g rice meal (Fig. 1). Due to the extraordinary body height and the resulting length of the esophagus, our manometry catheter was too short to completely cover the tubular esophagus and LES and hence accurately determine the integrated relaxation pressure. Bolus stasis was imminent on impedance testing. A complementary endoFLIP analysis verified restricted and pathologic distensibility of the EGJ of 2.1 mm^2/ mmHg (Fig. 2 A). Compatible with these results a Barium swallow demonstrated stagnant contrast medium column in the distal esophagus after 1, 3 and 5 minutes (Fig.3 A).

DIFFERENTIAL DIAGNOSIS ***If relevant***

TREATMENT and OUTCOME ***If relevant***

Based on the results that suggest the presence of achalasia type II, the therapeutic options were presented to the patient. Upon request, we performed a pneumatic dilation. At first, we used a 30mm Rigiflex balloon dilating the EGJ for 1 minute with 20 PSI under fluoroscopic control to minimize the risk for esophageal perforation followed by a 35mm Rigiflex balloon dilation 3 months later. Progress monitoring with a barium swallow and improvement of the Eckardt score confirmed the successful intervention (Fig. 3 B, Table 1). Moreover, during the second dilation, no more esophageal candidiasis was observed.

	Weight loss (kg)	Dysphagia	Retrosternal pain	Regurgitation	Total score
Before first dilation	0	0	3	0	3
After sec. Dilation	0	0	1	0	1

Table 1: Eckardt score before and after dilation treatment

OUTCOME AND FOLLOW-UP

In a 2 month follow up, the patient was doing significantly better and only complained of infrequent retrosternal cramps of mild intensity and an occasional feeling of a slow passage of food through the esophagus. Subjectively, the patient described an 80 – 90% improvement of symptom severity. Follow up by symptom assessment and barium swallow is planned in 12 months.

DISCUSSION ***Include a very brief review of similar published cases***

The above described case of achalasia is in several ways remarkable: At first, our patient has a history of GBS. After an extensive literature review we could find 3 cases reporting onset of achalasia with or after the development of a GBS[10-12]. A common

pathogenesis or a causal relationship, however, remains to be elucidated.

Both diseases are rare and a concomitant appearance in one individual patient estimated to be unlikely[12]. Mechanistically, a common autoimmune mechanism, potentially triggered by a gastroenteritis or respiratory tract infection is discussed as trigger in the literature[10-13]. In our case, there was a long duration of approximately 4 years between the GBS and the onset of the first symptoms of achalasia. This could be presumably explained by a very slow disease progression with relatively mild symptoms, which remained atypical until our diagnosis 12 years later. Further, purely speculative and without any literature data, a “late onset GBS associated achalasia” could be proposed in our patient.

Secondly, the patient presented with unusual symptomatology: The major complaint was an intermittent feeling of retrosternal cramps for years mainly independent of food intake and accompanied with recurrent esophageal candidiasis. There were no other classical symptoms of achalasia such as dysphagia, regurgitation or weight loss reported. This proved to be of relevance in two ways. On the one hand, the atypical presentation can be considered accountable for the long duration of about 7 years with numerous diagnostic workups till the correct diagnosis was finally made. It clearly demonstrates, that achalasia should be considered as a rare differential diagnosis of recurrent esophageal candidiasis with retrosternal cramps. Furthermore, it is interesting to note here that the esophageal candidiasis completely vanished after the dilation treatment making it likely that the candidiasis was caused by the persistent esophageal stasis associated with the impaired relaxation of the lower esophageal sphincter. On the other hand the atypical symptomatology showed that the Eckardt Score, which has so far been established as a useful disease severity scoring tool[14], does have certain limitations especially if atypical symptomatology of achalasia results in a very low initial score. This makes usage of the Eckardt score also problematic if monitoring of therapeutic success is intended (table 1).

Thirdly, due to the patient’s extraordinary body height and the resulting length of the esophagus, the HRIM catheter was too short to fully cover the LES region. Hence, apart from aperistalsis and panesophageal pressure increase upon swallowing other parameters, such as the IRP, could not be precisely determined. However, according to

current classification, the diagnosis of achalasia requires the detection of complete aperistalsis along with impaired deglutitive relaxation of the LES with an IRP > 15 mmHg[8]. By using the endoFLIP technology as a supplementary tool we could further evaluate the EGJ and by detecting a pathologic distensibility secure the diagnosis (Fig. 2A). In comparison, a normal distensibility of the EGJ can be observed in a healthy esophagus (Fig. 2B). This demonstrate that endoFLIP is a powerful supplementary tool to further characterize esophageal motility disorders especially in cases where technical limitations of HRIM hamper a correct diagnosis.

LEARNING POINTS/ TAKE HOME MESSAGES ***3 to 5 bullet points – this is a required field***

- The pathogenesis of the Guillain-Barré-Syndrome and achalasia might share common autoimmune and neurodegenerative processes
- Achalasia should be considered as a rare differential diagnosis in recurrent esophageal candidiasis
- In achalasia with asymptomatic presentation, the Eckardt Score might be an insufficient tool in assessing disease severity and in monitoring the treatment success
- EndoFLIP is a novel and useful tool to evaluate the distensibility of the EGJ especially in cases where HRIM does not show clear results or where the HRIM catheter is not well tolerated.

REFERENCES ***Vancouver style (Was the patient involved in a clinical trial? Please reference related articles)***

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FIGURE/ VIDEO CAPTIONS ***figures should NOT be embedded in this document***

Fig. 1: A) HRIM Clouse plot showing aperistalsis and panesophageal pressure increase instantaneously upon water swallows. Due to the significant length of the esophagus, both esophageal sphincters cannot be completely covered by the catheter. Hence important HRIM parameters such as the IRP could not be precisely determined. B) Combined HRIM Clouse and impediance plot showing aperistalsis and ineffective clearance during the rice meal.

Fig. 2: A) EndoFLIP analysis showing a restricted and pathologic distensibility of the

EGJ. B) In Comparison, a non-pathologic distensibility of a normal EGJ.

Fig. 3: A) Barium swallows showing an impaired relaxation of the LES as well as a stagnant contrast medium column in the distal esophageus after 5 minutes B) After the second dilation a significantly improved passage of the contrast medium through the EGJ and no stagnant column after 5 minutes could be observed.

PATIENT'S PERSPECTIVE ***Optional but strongly encouraged – this has to be written by the patient or next of kin***

PLEASE SAVE YOUR TEMPLATE WITH THE FOLLOWING FORMAT:

Corresponding author's last name and date of submission, eg,

Smith_September_2014.doc